

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>Case 20341</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 00/ 00847</b>	International filing date (day/month/year) <b>03/02/2000</b>	(Earliest) Priority Date (day/month/year) <b>04/02/1999</b>
Applicant <b>ROCHE DIAGNOSTICS GMBH et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

## 4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

## 5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1  
☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 00/00847

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-10 in part  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10 in part

Present claims 1-10 relate to an extremely large number of possible compositions. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compositions prepared in the examples, those specifically claimed, and to the process of their preparation.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 00/00847

## Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The object of the invention is to provide a pharmaceutical composition of a hydrophobically modified hedgehog protein containing a biocompatible carrier, wherein the carrier binds the hedgehog protein as an active folded structure and can release it locally in vivo in an active form in a delayed manner. Such formulations are particularly suitable for the repair of bone and cartilage defects and can also be used to repair neuronal defects or for a systemic delivery.

The object is achieved by a pharmaceutical composition of a hydrophobically modified hedgehog protein which is characterised in that this composition contains hydrophobically modified hedgehog proteins and a biodegradable protein or a proteolytic degradation product thereof as a carrier.

# INTERNATIONAL SEARCH REPORT

International Application No  
**PCT/EP 00/00847**

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7    **A61K47/48**    **A61K9/16**    **A61K38/17**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7    **A61K**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PORTER ET AL: "Cholesterol modification of hedgehog signaling proteins in animal development" SCIENCE, vol. 274, no. 2, 11 October 1996 (1996-10-11), pages 255-259, XP002082038 figure 1	1-10
X	BLAKE PEPINSKI R ET AL: "Identification of a palmitic acid-modified form of human sonic hedgehog" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 22, 29 May 1998 (1998-05-29), pages 14037-14045, XP002094956 abstract * Absatz DISCUSSION *	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

**13 March 2000**

Date of mailing of the international search report

**20/03/2000**

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

**Dullaart, A**

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 00/00847

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 90 08551 A (DAMON BIOTECH INC) 9 August 1990 (1990-08-09) example 2	1-10
Y	KIKUCHI A ET AL: "Pulsed dextran release from calcium-alginate gel beads" JOURNAL OF CONTROLLED RELEASE, vol. 47, no. 1, 7 July 1997 (1997-07-07), page 21-29 XP004091190 paragraph '02.2! figures 3-5 * Absatz DISCUSSION *	1-10
Y	ROBINSON C J: "Neurotrophic factors - novel therapeutics" TRENDS IN BIOTECHNOLOGY, vol. 14, no. 12, December 1996 (1996-12), page 451-452 XP004071034 page 452, middle column	1-10
Y	DOWNS E.C. ET AL: "Calcium alginate beads as a slow-release system for delivering angiogenic molecules in vivo and in vitro" J. CELL. PHYSIOL., 1992, VOL. 152, NO. 2, PAGE(S) 422-429, XP002072808 abstract page 423 page 427	1-10
Y	GRAY, C. J. ET AL: "Retention of insulin in alginate gel beads" BIOTECHNOL. BIOENG., 1988, VOL. 31, NO. 6, PAGES 607-612, XP002072809 tables 1,2 page 609, paragraph R * Absatz DISCUSSION *	1-10
X	Y. YANG ET AL.: "Relationship between dose, distance and time in Sonic Hedgehog-mediated regulation of anteroposterior polarity in the chick limb" DEVELOPMENT, vol. 124, 1997, pages 4393-4404, XP002072810 cited in the application abstract page 4394, right-hand column table 1B figures 1-3 tables 2,3,'B	1-10
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## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/EP 00/00847

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. LÓPEZ-MARTÍNEZ ET AL: "Limb-patterning activity and restricted posterior localization of the amino-terminal product of Sonic hedgehog cleavage" CURRENT BIOLOGY, vol. 5, no. 7, 1995, pages 791-796, XP002072811 cited in the application abstract page 794 page 197, left-hand column, last paragraph	1-10
X	E. MARTÍ ET AL.: "Requirement of 19K form of Sonic hedgehog for induction of distinct ventral cell types in CNS explants" NATURE, vol. 375, 25 May 1995 (1995-05-25), pages 322-325, XP002072812 LONDON, GB cited in the application abstract page 323, left-hand column page 325 figures	1-10
Y	M.J. BITGOOD ET AL.: "Sertoli cell signaling by Desert hedgehog regulates the male germline" CURRENT BIOLOGY, vol. 6, no. 3, 1996, pages 298-304, XP002072813 cited in the application page 300, right-hand column, last paragraph -page 303	1-10
Y	N. KINTO ET AL.: "Fibroblasts expressing Sonic hedgehog induce osteoblast differentiation and ectopic bone formation" FEBS LETTERS., vol. 404, 1997, pages 319-323, XP002072814 AMSTERDAM NL cited in the application paragraph 'RESULTS!'	1-10
Y	WO 94 08599 A (UNIV COLORADO) 28 April 1994 (1994-04-28) examples	1-10

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/00847

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PORTER ET AL: "Hedgehog patterning activity: Role of a lipophilic modification mediated by the carboxy-terminal autoprocessing domain" CELL, vol. 86, no. 4, 12 July 1996 (1996-07-12), pages 21-34, XP002082039 paragraph 'RESULTS!; figure 5	1-10
Y	HAMMERSCHMIDT M ET AL: "The world according to hedgehog" TRENDS IN GENETICS, vol. 13, no. 1, 1 January 1997 (1997-01-01), page 14-21 XP004015059 figure 1 page 19 -page 20	1-10
Y	FARESE R V ET AL: "Cholesterol metabolism and embryogenesis" TRENDS IN GENETICS, vol. 14, no. 3, 1 March 1998 (1998-03-01), page 115-120 XP004108610 page 119 -page 120	1-10
Y	YOSHIHIRO KAWAGUCHI ET AL: "CONFORMATIONAL CHANGES OF HYALURONATES WITH PARTIAL PALMITOYLATION AND THE ADSORPTION STRUCTURES ON THE SURFACE OF OIL DROPLETS" CARBOHYDRATE POLYMERS, vol. 20, no. 3, 1 January 1993 (1993-01-01), pages 183-187, XP000364403 abstract paragraph 'RESULTS!	1-10
Y	YOSHIHIRO KAWAGUCHI ET AL: "THE EFFECTS OF POLYSACCHARIDE CHAIN-LENGTH IN COATING LIPOSOMES WITH PARTIAL PALMITOYL HYALURONATES" CARBOHYDRATE POLYMERS, vol. 18, no. 2, 1 January 1992 (1992-01-01), pages 139-142, XP000262518 abstract paragraph 'RESULTS!	1-10

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 00/00847

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ILLUM L ET AL: "HYALURONIC ACID ESTER MICROSPHERES AS A NASAL DELIVERY SYSTEM FOR INSULIN" JOURNAL OF CONTROLLED RELEASE, vol. 29, no. 1/02, 1 February 1994 (1994-02-01), pages 133-141, XP000433658 paragraph 'RESULTS! * Absatz DISCUSSION *	1-10
P,X	EP 0 947 201 A (ROCHE DIAGNOSTICS GMBH HRB 396) 6 October 1999 (1999-10-06) examples figures	1-10
P,Y	EP 0 953 576 A (ROCHE DIAGNOSTICS GMBH) 3 November 1999 (1999-11-03) examples	1-10
E	EP 0 978 285 A (HOFFMANN LA ROCHE) 9 February 2000 (2000-02-09) example 3 claims	1-10

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/00847

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9008551	A	09-08-1990	AU 5107490 A CA 2046324 A EP 0457837 A JP 4502768 T	24-08-1990 27-07-1990 27-11-1991 21-05-1992
WO 9408599	A	28-04-1994	AU 5171293 A US 5981474 A US 5770559 A	09-05-1994 09-11-1999 23-06-1998
EP 0947201	A	06-10-1999	AU 713568 B AU 1542699 A CN 1228994 A CZ 9900337 A HR 990036 A HU 9900251 A NO 990471 A PL 331201 A	02-12-1999 26-08-1999 22-09-1999 11-08-1999 31-08-1999 28-09-1999 05-08-1999 16-08-1999
EP 0953576	A	03-11-1999	EP 0953575 A AU 2500999 A CN 1233616 A NO 992090 A PL 332894 A	03-11-1999 11-11-1999 03-11-1999 01-11-1999 08-11-1999
EP 0978285	A	09-02-2000	NONE	

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C. 20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 27 September 2000 (27.09.00)	<b>Applicant's or agent's file reference</b> Case 20341
<b>International application No.</b> PCT/EP00/00847	<b>Priority date</b> (day/month/year) 04 February 1999 (04.02.99)
<b>International filing date</b> (day/month/year) 03 February 2000 (03.02.00)	
<b>Applicant</b> PAPADIMITRIOU, Apollon et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 02 August 2000 (02.08.00)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b> Charlotte ENGER Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WACHENFELD, Joachim  
Vossius & Partner  
P.O. Box 86 07 67  
81634 München  
ALLEMAGNE

<b>Date of mailing (day/month/year)</b> 18 January 2001 (18.01.01)	<b>IMPORTANT NOTIFICATION</b>
<b>Applicant's or agent's file reference</b> E 3000 PCT	
<b>International application No.</b> PCT/EP00/00847	<b>International filing date (day/month/year)</b> 03 February 2000 (03.02.00)

<b>1. The following indications appeared on record concerning:</b> <input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative		
<b>Name and Address</b> SCHREINER, Siegfried Roche Diagnostics GmbH Patent Department Pharma (TR-E) P.O. Box 11 52 D-82372 Penzberg Germany	<b>State of Nationality</b>	<b>State of Residence</b>
	<b>Telephone No.</b> 08856/60-3446	
	<b>Facsimile No.</b> 08856/60-3451	
	<b>Teleprinter No.</b>	
<b>2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:</b> <input type="checkbox"/> the person <input checked="" type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence		
<b>Name and Address</b> WACHENFELD, Joachim Vossius & Partner P.O. Box 86 07 67 81634 München Germany	<b>State of Nationality</b>	<b>State of Residence</b>
	<b>Telephone No.</b> +49-89-41 30 40	
	<b>Facsimile No.</b> +49-89-41 30 41 11	
	<b>Teleprinter No.</b>	
<b>3. Further observations, if necessary:</b>  		
<b>4. A copy of this notification has been sent to:</b> <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the designated Offices concerned <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the elected Offices concerned <input checked="" type="checkbox"/> the International Preliminary Examining Authority <input type="checkbox"/> other:		

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b> J. Leitao Telephone No.: (41-22) 338.83.38
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